Microarray Technologies

The most exciting technology in genetics research? The DNA chip of course, featured in the pages of *The New York Times, Fortune,* and other media aimed at movers and shakers.

But the chip, a miniature marvel for analyzing DNA, is just one of a group of technologies known as microarrays. Microarrays are large numbers of parallel elements (often, but not always, DNA) grouped in a very small space for computer analysis.

Scientists at the DIR's Cancer Genetics Branch (CGB) have been refining one microarray method and using it to study cancer since 1996. Their arrayer robot positions functional gene fragments so precisely that today more than 10,000 can fit on a portion of an ordinary microscope slide. DNA probes labeled with fluorescence are then placed on the slide to hybridize with their complements among the fragments, each of which represents a particular human gene. The slide is put into a scanner that measures the brightness of each fluorescent dot, an indication of gene activity. Computer analysis of gene activity patterns allows scientists to compare the pattern of gene expression between normal and diseased cells.

Recently CGB researchers have used the system to study a frequently fatal childhood cancer called alveolar rhabdomyosarcoma (ARMS) and discovered that its cells have a characteristic gene-expression "fingerprint". The pattern distinguishes those tumor cells from other cancers, even when the samples come from different patients.

Such research studies are hoped ultimately to be useful for diagnosis or for explaining in detail what goes on in a tumor cell, according to Michael Bittner, who heads the Teleonomics Unit of the CGB. "However, to really get an insight into those questions, we're going to have to examine a very large number of samples. As it is, not having had any ability of this kind up until now, we have only the very dimmest sense of how the genes interact with each other and what genes are on what pathway," he points out.

The CGB is collaborating with other researchers in investigating the effects of disease viruses on gene expression in the host's cells. Viruses under study include HIV and the Ebola virus.

A major aim of this work is to answer controversial questions about the role of viruses in cancers and autoimmune diseases.

The lab intends to continue characterizing gene expression in different kinds of tumor tissues. Bittner wonders, for example, how many different cancers are hiding out under the single term "breast cancer?"

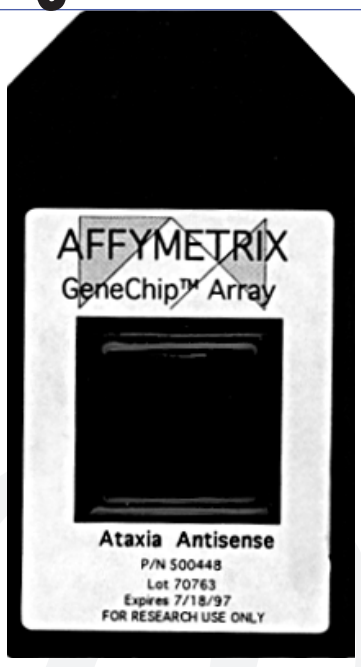
The scientists also plan to look at more general genetic questions such as which genes are expressed all the time at fairly constant levels no matter what kind of cell they're from. Or conversely, which genes vary a lot depending on what the cell is doing currently in life.

The better-known gene chip—a piece of glass the size of a postage stamp enclosed in a black plastic case—is getting a workout at the DIR's Genetics and Molecular Biology Branch. In collaboration with the chip's maker Affymetrix, the lab has already used the chip experimentally to look for alterations in large genes like the breast cancer genes BRCA1 and BRCA2, both in humans and in our closest relatives, chimpanzees and gorillas.

The scientists have recently turned their attention to Atm, the gene for ataxia-telangiectasia (AT) that was discovered at the DIR in 1995. AT is a rare fatal disease. Children with AT are predisposed to cancer and exceptionally sensitive to radiation.

AT occurs when a child inherits two altered Atm genes, one from each parent. Although each possesses a single mutant gene, the parents (called carriers) do not have AT. But there is a strong suspicion that carriers also run a three- to four-fold increased risk of cancer.

"Because so many people carry alterations in the Atm gene, even if the risk associated with being a carrier turns out to be low, it could become a public health consideration because of the large number of people it would affect," says Joseph

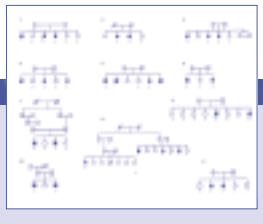


Hacia, who supervises the chip project. Carrier frequency of the mutant gene has been roughly estimated at 1% of the population, more than 2.5 million people in the U.S. alone.

With the first chip containing the huge Atm gene, the scientists found they could detect about 91% of altered genes present. The chip's design has since been improved. "What we're hoping is that instead of being 91% accurate we're going to be closer to 95% accurate, or perhaps higher," Hacia reports.

That accuracy range, he points out, is still not optimal for clinical use. But it is accurate enough for population studies on historical tissue samples. Such retrospective surveys could make carrier estimates more accurate. And, if their risk of cancer turns out to be higher than in noncarriers, the studies could reveal just what that risk is. ●

http://www.nhgri.nih.gov/DIR/VIP/Learning_Tools/research_technique.html



June, 1994
FUSION project to study the incidence of Type II diabetes in the Finnish population started.

September, 1994
Location of the gene for Wolfram syndrome determined.

September, 1994
Germline p16 mutations in familial melanoma reported.